WHAT IS CLAIMED IS:

1. A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:

(a) identifying, within a target protein or peptide, one or more target amino acids amenable to providing the evolved predetermined property or activity upon amino acid replacement, wherein each target amino acid is designated an *in silico*-HIT (is-HIT);

(b) identifying one or more replacement amino acids, specific for each is-HIT, amenable to providing the evolved predetermined property or activity to the target protein upon amino acid replacement, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;

(c) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein:

each candidate LEAD protein contains a single amino acid replacement;

each nucleic acid in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide'

each set is separate from all other sets;

(d) introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are in an addressable array such that each lead protein is expressed at a different locus in the array;

(e) individually screening the sets of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such protein is designated a LEAD mutant protein.

2. The method of claim 1, wherein the array comprises a solid support with separate loci and each set of cells is at a different locus.

3. The method of claim 2, wherein the loci comprise wells; and each well contains one set of cells.

4. The method of claim 1, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids or are bacterial cells are transformed with the plasmids.

5. The method of claim 1, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

6. The method of claim 1, further comprising:

(f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

(g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

(h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

7. The method of claim 6, wherein the nucleic acid molecules in step (f) are produced by a method selected from among Additive Directional Mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

8. The method of claim 1 wherein the is-HITs identified in step (a) correspond to a restricted subset of amino acids along the full length target protein.

9. The method of claim 1, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

10. The method of claim 1, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining

amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

11. The method of claim 6, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

12. The method of claim 1, wherein the change in activity is at least about 10% of the activity of the unmodified target protein.

13. The method of claim 1, wherein the change in activity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, of the activity of the unmodified target protein.

14. The method of claim 1, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater than the activity of the unmodified target protein.

15. The method of claim 1, wherein the activity modified is selected from among increased catalytic activity, altered substrate and ligand recognition, increased thermostability, increased stability, increased resistance to proteases, increased resistance to glomerular filtration, increased immunogenicity, increased cationization, increased anionization and pseudo wild-type function.

16. The method of claim 1, wherein each is-HIT target amino acid is susceptible to digestion by one or more proteases.

17. The method of claim 16, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

18. The method of claim 1, wherein in a modified protein, each is-HIT target amino acid is resistant to digestion by one or more proteases compared to in unmodif protein.

19. The method of claim 18, wherein the LEADs or super-LEADs possess increased digestibility compared to unmodified target protein.

20. The method of claim 1, wherein each is-HIT target amino acid affects protein conformation and/or antigenicity.

21. The method of claim 20, wherein the LEADs or super-LEADs possess either increased or decreased antigenicity compared to unmodified target protein.

22. The method of claim 1, wherein each is-HIT target amino acid affects protein amphipathic properties.

23. The method of claim 22, wherein the LEADs or super-LEADs possess either increased or decreased amphipathic properties compared to unmodified target protein.

24. The method of claim 1, wherein each is-HIT target amino acid is amenable to constitute a link or bridge between two regions of a protein.

25. The method of claim 24, wherein the LEADs or super-LEADs possess increased thermostability compared to unmodified target protein.

26. The method of claim 1, wherein each is-HIT target amino acid affects binding affinity to its cognate receptor.

27. The method of claim 26, wherein the LEADs or super-LEADs possess either increased or decreased binding affinity to its cognate receptor compared to unmodified target protein.

28. A method for generating proteins with a desired property, comprising:

(a) identifying a target protein;

(b) identifying is-HIT target residues associated with the property;

(c) preparing a collection of variant nucleic acid molecules encoding a collection of variant proteins, wherein each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid from the target protein at one is-HIT target residue;

(d) separately introducing the nucleic acids encoding each candidate LEAD protein into hosts for expression thereof and expressing the nucleic acid molecules encoding each variant protein;

(e) screening each variant LEAD candidate proteins to identify any that have an activity that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

29. The method of claim 28, wherein either: each of the identified is-HIT target residues in the target protein is replaced with codons encoding a restricted subset of the remaining 19 amino acids; or the total number of is-HIT residues that are replaced with replacement amino acids is less than the total amount of amino acid residues within the full-length of the target protein.

30. The method of claim 28, wherein each of the identified is-HIT residues in the target protein is replaced with codons encoding a restricted subset of the remaining 19 amino acids.

31. The method of claim 28, wherein the total number of is-HIT residues that are replaced with replacement amino acids is less than the total amount of amino acid residues within the full-length of the target protein.

32. The method of claim 28, wherein each of the identified is-HIT residues in the target protein is replaced with codons encoding a restricted subset of the remaining 19 amino acids; and the total number of is-HIT residues that are replaced with replacement amino acids is less than the total amount of amino acid residues within the full-length of the target protein.

33. The method of claim 28, further comprising:

(d) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

(e) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

(f) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

34. The method of claim 33, wherein the nucleic acid molecules in step (f) are produced by a method selected from among additive directional mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

35. The method of claim 33, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

36. The method of claim 28, wherein each is-HIT target residue is susceptible to digestion by one or more proteases.

37. The method of claim 36, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

38. The method of claim 28, wherein each is-HIT target residue is resistant to digestion by one or more proteases.

39. The method of claim 38, wherein the LEADs or super-LEADs possess increased digestibility compared to unmodified target protein.

40. The method of claim 28, wherein each is-HIT target residue affects protein conformation.

41. The method of claim 40, wherein the LEADs or super-LEADs possess either increased or decreased antigenicity compared to unmodified target protein.

42. The method of claim 28, wherein each is-HIT target amino acid affects protein amphipathic properties.

43. The method of claim 42, wherein the LEADs or super-LEADs possess either increased or decreased amphipathic properties compared to unmodified target protein.

44. The method of claim 28, wherein each is-HIT target amino acid is amenable to constitute a link or bridge between two regions of a protein.

45. The method of claim 44, wherein the LEADs or super-LEADs possess increased thermostability compared to unmodified target protein.

46. The method of claim 28, wherein each is-HIT target amino acid affects binding affinity to its cognate receptor.

47. The method of claim 46, wherein the LEADs or super-LEADs possess either increased or decreased binding affinity to its cognate receptor compared to unmodified target protein.

48. The method of claim 28, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, of the activity of the unmodified target protein.

49. The method of claim 28, wherein the change inactivity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, of the activity of the unmodified target protein.

50. The method of claim 28, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times,

500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater than the activity of the unmodified target protein.

51. A method for the production of a protein having an evolved property or activity compared to a unmodified target protein, the method comprising:

(a) selecting, on the target protein, one or more target amino acids amenable to providing the evolved property or activity upon amino acid replacement;

(b) replacing each target amino acid with a replacement amino acid amenable to providing the evolved property or activity to form a candidate LEAD protein, wherein only one amino acid replacement occurs on each target protein;

(c) expressing from a nucleic acid molecule each candidate LEAD protein in a cell contained in an addressable array; and

(d) assaying each candidate LEAD protein for the presence or absence of the evolved property or activity compared to a unmodified target protein, thereby identifying proteins that are LEADs.

52. The method of claim 51, wherein the selection of the one or more target amino acids in step a) is conducted *in silico* and the targets amino acids are designated is-Hits.

53. The method of claim 52, wherein the *in silico* selection step further comprises selecting an is-HIT target residue that is susceptible to digestion by one or more proteases.

54. The method of claim 53, wherein the LEADs possess increased resistance to proteolysis compared to unmodified target protein.

55. The method of claim 52, wherein the *in silico* selection step further comprises selecting an is-HIT target residue is resistant to digestion by one or more proteases.

56. The method of claim 55, wherein the LEADs possess increased digestibility compared to unmodified target protein.

57. The method of claim 52, wherein the *in silico* selection step further comprises selecting an is-HIT target residue affects protein conformation and/or immunogenicity.

58. The method of claim 57, wherein the LEADs possess either increased or decreased antigenicity compared to unmodified target protein.

59. The method of claim 51, wherein the *in silico* selection step further comprises selecting an is-HIT target amino acid affects protein amphipathic properties.

60. The method of claim 59, wherein the LEADs possess either increased or decreased amphipathic properties compared to unmodified target protein.

61. The method of claim 60, wherein the *in silico* selection step further comprises selecting an is-HIT target amino acid is amenable to constitute a link or bridge between two regions of a protein.

62. The method of claim 61, wherein the LEADs possess increased thermostability compared to unmodified target protein.

63. The method of claim 62, wherein the *in silico* selection step further comprises selecting an is-HIT target amino acid affects binding affinity to its cognate receptor.

64. The method of claim 63, wherein the LEADs possess either increased or decreased binding affinity to its cognate receptor compared to unmodified target protein.

65. The method of claim 51, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, of the activity of the unmodified target protein.

66. The method of claim 51, wherein the change inactivity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, of the activity of the unmodified target protein.

67. The method of claim 51, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times,

9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater than the activity of the unmodified target protein.

68. A method of displaying the amino acid sequence of a protein, said method comprising:

providing a first axis that corresponds to amino acid positions along the length of the protein sequence, wherein each amino acid position is designated as a position-cell;

providing a second axis at each amino acid position within said protein, wherein said second axis contains 20 type-cells thereon, wherein each type-cell corresponds to a mutually exclusive amino acid; and

indicating the particular amino acid residue at the respective cell-type/position-cell intersection by a detectable signal.

69. The method of claim 68, wherein the number of position-cells is variable depending on the size of the protein.

70. The method of claim 68, wherein the number of position-cells equals the number of amino acids in the protein sequence.

71. The method of claim 68, wherein the first axis is vertical and the second axis is horizontal.

72. A medium, comprising a matrix display produced by the method of claim 68.

73. The medium of claim 72 that is can be read visually or that is computer readable.

74. A two-dimensional (2-D) matrix representation of a protein sequence comprising:

a first axis that corresponds to amino acid positions along the length of the protein sequence, wherein each amino acid position is designated as a position-cell;

a second axis at each amino acid position within said protein, wherein said second axis contains 20 type-cells thereon, wherein each type-cell corresponds to a mutually exclusive amino acid; and

an indentifier indicating the particular amino acid residue at the respective cell-type/position-cell intersection.

75. A method for making a modified protein having substantially the same activity as unmodified protein, the method comprising:

replacing each amino acid position over the entire length of a target protein with the same reference amino acid, wherein only one reference amino acid is substituted on each molecule, to form a candidate HIT;

assaying each candidate HIT for a change in a selected protein activity;

identifying each locus on the target protein that is amenable to amino acid replacement without change in the protein activity as a pseudo-wild type position.

76. The method of claim 75, further comprising replacing one or more pseudo-wild type positions with candidate pseudo-wild type amino acids, wherein an amino acid replacement that does not result in a decrease in the requisite protein activity is designated a pseudo-wild type amino acid at that pseudo-wild type position.

77. The method of claim 76, wherein the change in a protein activity is a decrease.

78. The method of claim 76, wherein at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 15%, at least 20%, at least 25%, of amino acid residue positions on a target protein are replaced.

79. The method of claim 1, wherein the replacing amino acids are selected using Percent Accepted Mutations (PAM) matrices.

80. The method of claim 1, wherein the replacing amino acids are pseudo-wild type amino acids.